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The number of possible structures of conformationally fixed O-alkylation products of calix[4]arenes

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O-Alkylation of calix[4]arenes leads to conformationally fixed derivatives provided the groups attached to the oxygen are large enough. In principle 34 different tetra-, 13 tri-, 8 dialkylation products may be obtained starting with a calix[4]arene consisting of four identical phenolic units. 17, 9 and 3 of these derivatives are inherently chiral.

There are various possible routes to inherently chiral calix[4]arene derivatives capable of existing as stable enantiomers.[1] One possibility is to attach (different) achiral groups to the phenolic oxygens, thus creating chirality (asymmetry) while simultaneously fixing the conformation. Examples for this type have been prepared mainly from the research groups of Shinkai[2] and Pappalardo.[3] The former recently undertook a systematic classification of all these possibilities,[4] which, however, is overly complicated, inconsistent, and in some parts erroneous. It is the aim of this paper to correct these mistakes and thus, to avoid further confusion.[5] Using Shinkai's notation A, B, C, D for phenolic residues carrying different alkoxy groups and H for a phenolic unit with a free OH group, and characterizing units pointing up and downwards in a graphical way by light and dark circles (or within the text by α and β as superscripts) we come to the classification given in Table 1. Thus we count

34 tetra-O-alkylated compounds, 17 of which are chiral (indicated by an asterisk),

13 tri-O-alkylated compounds, 9 of which are chiral, and

8 di-O-alkylated compounds, 3 of which are chiral.

(Shinkai's numbers for the chiral compounds were 24, 10, 3, while his indications for the total number of alkylation products are somewhat unclear).

It is also interesting to note, that with just one type of residue 12 different O-alkylation products (mono to tetra) are possible, 2 of which are chiral.

The following explanations will clarify our notation and emphasize its differences from Shinkai's classification:

(a) For H neither "up" nor "down" is indicated, if stereoisomers (existing as different separable species) are described, since the OH-group can pass through the annulus. For symmetry considerations it may be regarded therefore to be "in plane".

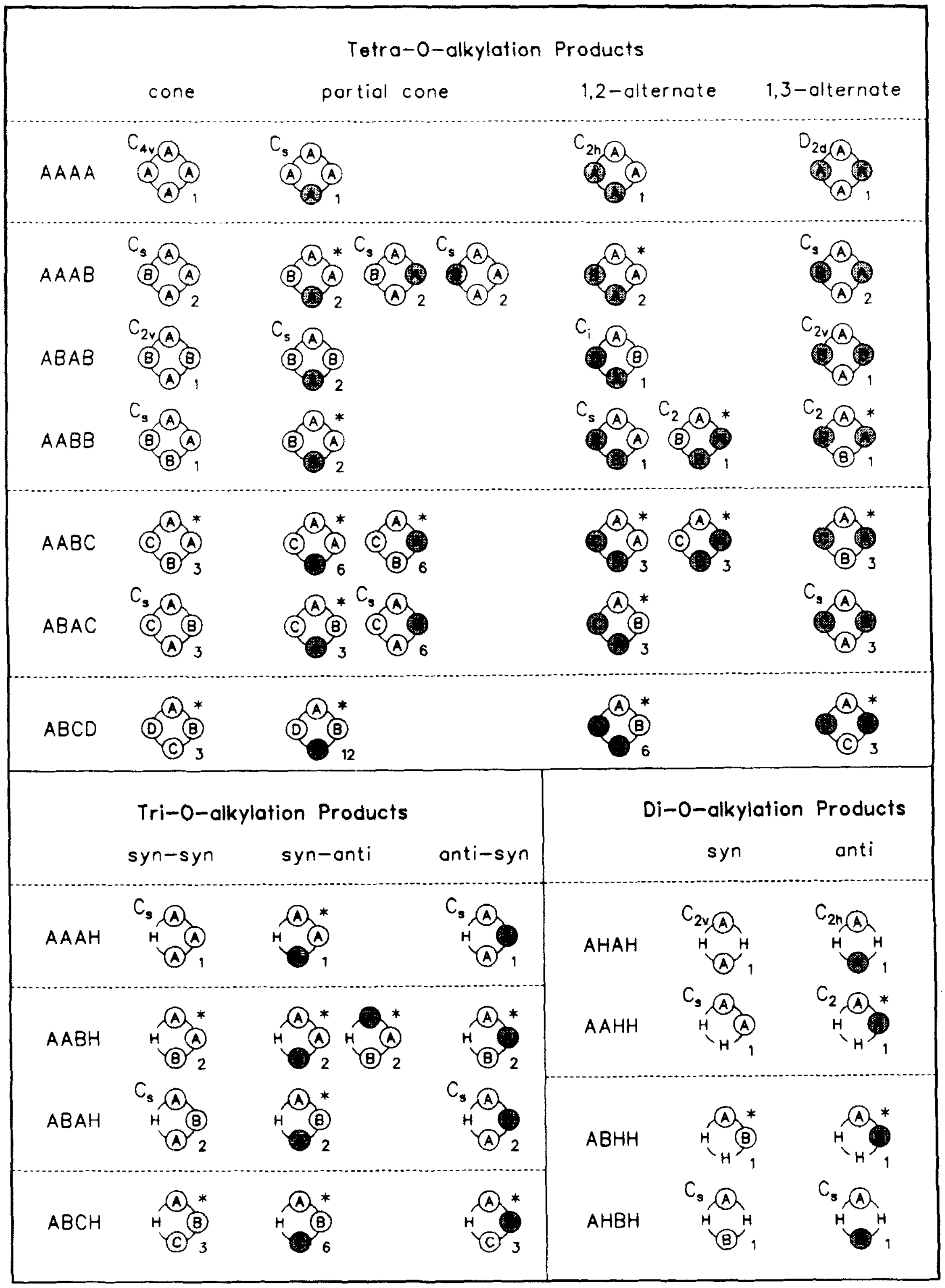
Thus for instance a tri-O-alkylated product with all alkoxy groups pointing in the same direction (*syn*, see below) can assume (at least in principle) the cone *and* the partial cone conformation, like the parent calix[4]-arene with free OH-groups in principle can assume all four conformations. In practice in both cases only the cone conformation is found.

The 1,2-*anti*-di-O-alkylated compound can assume partial cone, 1,2- and 1,3-alternate conformations[6] and the 1,3-*anti*-di-O-alkylated compound, partial cone and 1,2-alternate conformations. In fact the latter in some cases obviously assumes a conformation "in between" these two possibilities with the phenolic units being coplanar on the NMR time scale,[7] an additional striking reason not to mix up "stereoisomer" with "conformation".

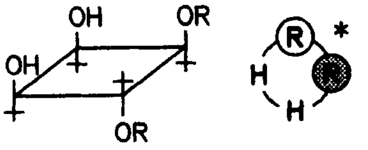
(b) For this reason the familiar expressions "cone", "partial cone", "1,2-alternate" and "1,3-alternate" are used and should be used only to describe the isomers of tetra-O-alkylated products, where they are unambiguous.

"Syn" and "anti" may be used in all other cases to describe the mutual situation of the alkoxy groups and

Table 1 Schematic representation of all types of tetra-, tri and di-O-alkylation products derivable for a calix[4]arene



For each type the symmetry group as well as the number of compounds available with the corresponding number of individual substituents are also reported. Asterisks indicate chiral derivatives.

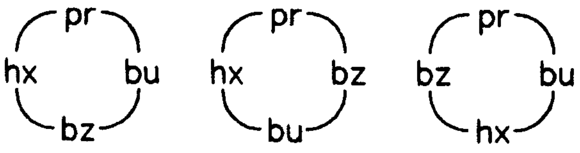


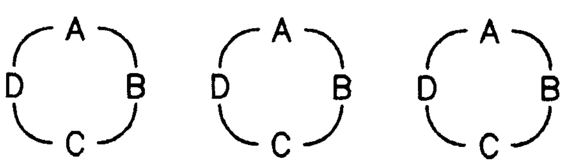
$R^{\alpha}\ R^{\beta}\ H\ H$

to characterize the possible derivatives (not their conformations, see above). Together with the α/β notation, we want to suggest this as a general rule for calix[4]arenes. In Table 1 we have used the expression *syn* and *anti* with respect to the first phenol ether unit in the sequence as reference (A on top of the graphical representation). If it would be used with respect to the immediately preceeding unit, the last column of the tri-O-alkylation products would be *anti-anti* instead of *anti-syn.*

(c) A, B, C and D are used to describe in general different types of O-alkylated units but not individual units.

Here are the main discrepancies in Shinkai's paper[4] which probably need further explanation. For four individual residues, e.g. propyl, butyl, benzyl, hexyl, three regioisomers exist:





They may be subsumed all under the same general formula ABCD (as shown above), but with different individual meanings for A, B, C and D. This is in accordance with Shinkai's classification. However, by this line of reasoning there is also *only one* partial cone isomer for the case ABCD (while Shinkai counts four) because always just *one of four* different residues points in the opposite direction than the other three. Regarding on the other hand the individual case, *each* of the three above mentioned regioisomers can form *four* stereoisomers in the partial cone conformation. Thus, 12 (!) different isomers with e.g. pr, bu, bz, hx can be obtained in principal in the partial cone conformation, each existing as a pair of enantiomers.

As another example we may regard the general class or type AAAB in the cone conformation which comprises for propyl and hexyl the two individual compounds pr, pr, pr, hx and hx, hx, hx, pr.

If we apply the above treatment to individual compounds, not just general classifications, the number of isomers would be much greater. The corresponding numbers are given also in Table 1. In summary[8] one gets:

93 tetra-O-alkylated compounds for up to four individual O-alkyl groups, 59 of which are chiral,

33 tri-O-alkylated compounds for up to three individual O-alkyl groups, 23 of which are chiral, and

8 di-O-alkylated compounds for up to two individual O-alkyl groups 3 of which are chiral.

We do not believe, that a tabulation of all these isomers as well as an extension of these considerations to calix[5]- and calix[6]-arenes would be helpful (at least not at the moment). On the other hand we hope, that misunderstandings can be avoided by the present paper, and that it may contribute to an unambiguous description of stereoisomers in the still growing field of calixarenes.

NOTES AND REFERENCES

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4 Iwamoto, K.; Shimizu, H.; Shinkai, S.; *J. Am. Chem. Soc.* **1993**, *115*, 3997.
5 On the recent XVIII International Symposium on Macrocyclic Chemistry (June 27–July 2, 1993, Enschede) S. Shinkai named the European research groups in the field of calixarenes "his friendly competitors", and it is in this friendly sense, that this publication should be understood.
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8 Even higher numbers would be obtained under the assumption that for the preparation of all the O-alkylation products a given set of four alkoxy substituents exists. Then for instance four compounds of the type AAAA in the cone conformation are possible.